



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



SARS-CoV-2 seroprevalence, and IgG concentration and pseudovirus neutralising antibody titres after infection, compared by HIV status: a matched case-control observational study

Matthew A Spinelli, Kara L Lynch, Cassandra Yun, David V Glidden, Michael J Peluso, Timothy J Henrich, Monica Gandhi, Lillian B Brown

Summary

Lancet HIV 2021; 8: e334-41

Published Online

April 29, 2021

[https://doi.org/10.1016/S2352-3018\(21\)00072-2](https://doi.org/10.1016/S2352-3018(21)00072-2)

See [Comment](#) page e312

Division of HIV, Infectious Diseases, and Global Medicine (M A Spinelli MD, M J Peluso MD, T J Henrich MD, Prof M Gandhi MD, L B Brown MD), Department of Laboratory Medicine (K L Lynch PhD, C Yun BS), and Department of Epidemiology and Biostatistics (Prof D V Glidden PhD), University of California, San Francisco, San Francisco, CA, USA

Correspondence to:

Dr Matthew A Spinelli, Division of HIV, Infectious Diseases, and Global Medicine, University of California, San Francisco, San Francisco, CA 94110, USA matthew.spinelli@ucsf.edu

Background Most cohorts show similar or lower COVID-19 incidence among people living with HIV compared with the general population. However, incidence might be affected by lower testing rates among vulnerable populations. We aimed to compare SARS-CoV-2 IgG seroprevalence, disease severity, and neutralising antibody activity after infection among people with and without HIV receiving care in a county hospital system over a 3-month period.

Methods In this matched case-control observational study, remnant serum samples were collected between Aug 1 and Oct 31, 2020, from all people living with HIV who underwent routine outpatient laboratory testing in a municipal health-care system (San Francisco General Hospital, CA, USA). Samples from people living with HIV were date of collection-matched (same day) and age-matched (± 5 years) to samples from randomly selected adults (aged 18 years or older) without HIV receiving care for chronic conditions at the same hospital. We compared seroprevalence by HIV status via mixed-effects logistic regression models, accounting for the matched structure of the data (random effects for the matched group), adjusting for age, sex, race or ethnicity, and clinical factors (ie, history of cardiovascular or pulmonary disease, and type 2 diabetes). Severe COVID-19 was assessed in participants with past SARS-CoV-2 (IgG or PCR) infection by chart review and compared with multivariable mixed-effects logistic regression, adjusting for age and sex. SARS-CoV-2 IgG, neutralising antibody titres, and antibody avidity were measured in serum of participants with previous positive PCR tests and compared with multivariable mixed-effects models, adjusting for age, sex, and time since PCR-confirmed SARS-CoV-2 infection.

Findings 1138 samples from 955 people living with HIV and 1118 samples from 1062 people without HIV were tested. SARS-CoV-2 IgG seroprevalence was 3.7% (95% CI 2.4 to 5.0) among people with HIV compared with 7.4% (5.7 to 9.2) among people without HIV (adjusted odds ratio 0.50, 95% CI 0.30 to 0.83). Among 31 people with HIV and 70 people without HIV who had evidence of past infection, the odds of severe COVID-19 were 5.52 (95% CI 1.01 to 64.48) times higher among people living with HIV. Adjusting for time since PCR-confirmed infection, SARS-CoV-2 IgG concentrations were lower (percentage change -53%, 95% CI -4 to -76), pseudovirus neutralising antibody titres were lower (-67%, -25 to -86), and avidity was similar (7%, -73 to 87) among people living with HIV compared with those without HIV.

Interpretation Although fewer infections were detected by SARS-CoV-2 IgG testing among people living with HIV than among those without HIV, people with HIV had more cases of severe COVID-19. Among people living with HIV with past SARS-CoV-2 infection, lower IgG concentrations and pseudovirus neutralising antibody titres might reflect a diminished serological response to infection, and the similar avidity could be driven by similar time since infection.

Funding US National Institute of Allergy and Infectious Diseases, US National Institutes of Health.

Copyright © 2021 Elsevier Ltd. All rights reserved.

Introduction

An understanding of whether susceptibility to SARS-CoV-2 infection or propensity to develop severe disease is increased in the population of people living with HIV is crucial for both these individuals and their health-care providers.¹ Although marginal housing can limit the ability of some people with HIV to shelter in place,² studies so far have found either similar³⁻⁶ or lower^{7,8} incidence of COVID-19 among people living with HIV compared with the general population, providing reassurance that HIV is

unlikely to be a risk factor for SARS-CoV-2 acquisition. People living with HIV might take greater caution due to higher perceived susceptibility, as well as experience of the HIV epidemic, leading to less exposure to SARS-CoV-2.¹ Conversely, persistent inflammation or lower CD4-to-CD8 cell ratios among people living with HIV than among those without HIV could increase susceptibility to viral infection.⁹

Defining the precise incidence of COVID-19 among people living with HIV has been challenging, given

Research in context

Evidence before this study

We searched PubMed for original research published in English between Jan 1, 2020, and Feb 21, 2021, with the search terms “HIV” AND “SARS-CoV-2” OR “COVID-19”. Previous large population-based studies found similar or lower SARS-CoV-2 incidence among people living with HIV compared with the general population, although this difference could be biased by differential testing rates among groups. One small previous seroprevalence study of a convenience sample included 270 people living with HIV in Umbria, Italy. No other systematic seroprevalence study for SARS-CoV-2 comparing people living with HIV to the general population had been published.

Added value of this study

In this matched case-control observational study, we tested for SARS-CoV-2 IgG using remnant samples among all people receiving outpatient laboratory testing in an HIV clinic from August to October, 2020. This group of people living with HIV was compared with an age-matched and date of collection-matched randomly selected sample of people without HIV from the same health-care system. We found approximately 50% lower

odds of past SARS-CoV-2 infection among people living with HIV than among those without HIV. However, more cases of severe COVID-19 occurred among people living with HIV than among those without HIV, and, among those with a previous positive PCR test, IgG concentrations were 53% lower and neutralising antibody titres were 67% lower among people living with HIV than among those without HIV.

Implications of all the available evidence

Our results support previous findings that people living with HIV do not seem to be at higher risk of SARS-CoV-2 infection than are those without HIV. However, evidence is growing that the risk of severe COVID-19 might be higher among people living with HIV who are exposed to SARS-CoV-2 than among the general population. Our results also raise concern that the serological immune response to natural infection could be blunted among people living with HIV, given lower neutralising antibody titres and IgG concentrations in this group. Future studies will need to follow up people living with HIV after natural infection to measure humoral and T-cell immune responses and ensure sufficient protection.

limitations in population-based data. In light of the high proportion of asymptomatic infections with SARS-CoV-2, incidence estimates could be biased by differential testing rates among populations.¹ Three of the largest population-based studies of COVID-19 incidence among people living with HIV (in Madrid [Spain], Barcelona [Spain], Wuhan [China], and New York State [USA]) showed similar or lower COVID-19 incidence among people living with HIV compared with those without HIV, although these studies did not report testing rates or test positivity.^{4,6–8} However, three US studies raised some concern for differential testing rates among people living with HIV.^{2,3} An integrated health system in Los Angeles (CA, USA) found a similar proportion of COVID-19 cases among people living with HIV and people without HIV, although the test positivity among people living with HIV was lower and the testing rate was higher, consistent with greater testing among people living with HIV.³ An analysis of the Veterans Aging Cohort study also showed similar infection incidence with a higher testing rate among people living with HIV than among those without.⁵ Conversely, a city-wide analysis in San Francisco (CA, USA) showed higher test positivity among people living with HIV than among those without, suggesting undertesting of people living with HIV, with more than half of HIV and SARS-CoV-2 co-infected individuals in that study experiencing marginal housing and unsuppressed viral loads.² Data on whether severe COVID-19 outcomes occur disproportionately among people living with HIV have suggested that more severe disease seems to occur at lower CD4 cell counts.^{6,10,11} Severe disease might also occur as a result of a greater number of comorbidities among people living with HIV.¹

Given the potential for a high degree of under-ascertainment of SARS-CoV-2 infection using PCR-based testing, population-based seroprevalence studies are needed to accurately determine attack rates. However, given the much smaller population of people living with HIV compared with the general population, and the challenge of doing clinical research during the ongoing pandemic, systematic seroprevalence studies comparing SARS-CoV-2 infection rates by HIV status have not yet been done, except a small seroprevalence study in Umbria (Italy).¹² We aimed to estimate SARS-CoV-2 seroprevalence among people with HIV compared with those without HIV. Given that IgG antibodies and neutralising antibody titres naturally decline following infection, we aimed to examine differences by HIV status in quantitative SARS-CoV-2 IgG concentrations, neutralising antibody titres, and antibody avidity among those with evidence of past infection, controlling for time since infection in the substratum with past PCR-confirmed infection.

Methods

Study design

In this matched case-control observational study, remnant serum samples from metabolic panels were collected between Aug 1 and Oct 31, 2020, from all people living with HIV who underwent routine outpatient laboratory testing at San Francisco General Hospital, which houses a large HIV clinic and supports a municipal health-care system. Each sample from people living with HIV was matched 1:1 by date of collection (same day) and age (± 5 years) to samples from randomly selected adults (aged 18 years or older) from internal medicine and

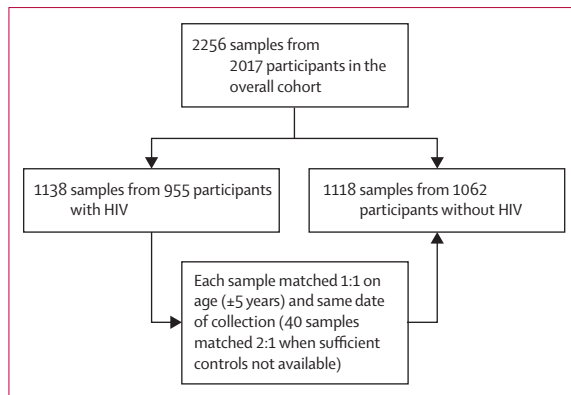


Figure 1: Flow diagram of matching process for participants and specimens enrolled in the study

family medicine clinics receiving outpatient metabolic panel laboratory testing in the same hospital, although 40 samples from people living with HIV were matched 2:1 when only a single suitable sample was available (figure 1). Because only remnant samples were used, and measures were taken to protect participant confidentiality, the University of California, San Francisco institutional review board did not require informed consent for study participation.

SARS-CoV-2 anti-RBD IgG measurement

SARS-CoV-2 antibody concentrations were quantified in serum with the Pylon COVID-19 IgG assay (ET HealthCare, Palo Alto, CA, USA), which targets the receptor-binding domain (RBD) of the spike protein. We used estimates for sensitivity of the IgG assay for past infection from an internal validation study with 79 outpatients and inpatients in the same health system (San Francisco General Hospital), with serum samples collected at least 3 weeks after PCR-confirmed infection. The RBD IgG assay showed 89% sensitivity for past infection among those with PCR-confirmed infection, which we used to estimate the adjusted seroprevalence in our study.¹³ As sensitivity of the IgG assay is not well established among individuals with a greater proportion of asymptomatic infection, we did a sensitivity analysis assuming 70% test sensitivity. Finally, the specificity of the RBD IgG assay was 100% using 80 blood donor specimens collected before June, 2018, so no adjustments were made for specificity in our analysis.¹³ In individuals with evidence of past infection, continuous IgG concentrations were measured and expressed in relative fluorescent units.

Pseudovirus neutralisation and antibody avidity

Pseudovirus neutralisation was measured with a label-free surrogate neutralisation assay (developed at a San Francisco General Hospital laboratory) that uses a thin-film interferometry immunoassay analyser.¹⁴ The label-free surrogate neutralisation assay measures the binding ability of the

SARS-CoV-2 RBD to the angiotensin converting enzyme 2 receptor after neutralising the RBD with antibodies in the serum. The neutralisation index is calculated as the ratio of binding ability of the RBD to the receptor after neutralisation to the full binding ability without neutralisation. The neutralising antibody titre is defined as the reciprocal of the dilution resulting in a 50% neutralisation index. Antibody avidity, a measure of the functional affinity of antibodies to the SARS-CoV-2 spike RBD, was assayed with previously described methods.¹⁵ Antibody avidity is calculated as the ratio of RBD-IgG–anti-IgG complexes measured after use of the dissociation agent (urea) to the reference (running buffer), presented as a percentage. IgG avidity typically increases with greater time since infection, although patients with COVID-19 requiring intensive care unit admission have higher avidity than those who do not.¹⁵

Clinical data

Medical conditions including type 2 diabetes, cardiovascular disease (including hypertension, cerebrovascular disease, coronary artery disease, and heart failure), chronic pulmonary disease (including chronic obstructive pulmonary disease, asthma, pulmonary hypertension, interstitial lung disease), and HIV were assessed using International Classification of Diseases (revision 10) codes downloaded from the medical record within the previous 6 months. Severe COVID-19, assessed via chart review, was defined as oxygen saturation of less than 94% on room air, respiratory rate of more than 30 breaths per min, or arterial partial pressure of oxygen/fractional concentration of oxygen in inspired air of more than 300 mm Hg. Experience of homelessness was assessed through clinic records and was available only for people living with HIV.

Statistical analysis

We adjusted absolute seroprevalence and 95% CIs for test sensitivity.¹⁶ We compared seroprevalence by HIV status via multivariable mixed-effects logistic regression models, accounting for the matched structure of the data (random effects for the matched group), adjusting for age (by 10 year age groups), sex, race or ethnicity, and clinical factors (ie, history of cardiovascular or pulmonary disease, and type 2 diabetes). In the HIV-specific model, HIV-specific factors were included: CD4 count (dichotomised at 200 cells per μ L), suppressed versus unsuppressed viral load (dichotomised at 200 copies per mL), and experience of homelessness. Severe COVID-19 among participants with evidence of past infection (IgG or PCR) was compared by HIV status with multivariable mixed-effects logistic regression, adjusting for age and sex, although profile likelihood CIs were used given very few outcomes. For participants with reactive SARS-CoV-2 IgG, we compared IgG concentrations (measured in relative fluorescent units) by HIV status with natural log-transformed mixed-effects linear models, adjusted for age and sex;¹⁷ the same process was repeated additionally adjusting for time since PCR-confirmed infection in participants with a previous positive PCR test. To

compare neutralising antibody titres among participants with past infection by HIV status, we used natural-log-transformed mixed-effects interval regression, adjusting for the same factors. To compare antibody avidity percentage by HIV status, we used a mixed-effects generalised linear model from the binomial distribution, adjusting for the same factors. The correlations among natural log-transformed IgG concentration, natural log-transformed pseudovirus neutralising antibody titres, and antibody percentage avidity were examined using Spearman's rank correlation. Statistical analyses were done with Stata SE (version 15.1) and graphs were made in R (version 4.0.5).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

1138 samples from 955 people living with HIV and 1118 samples from 1062 people without HIV were tested (figure 1; table 1). 103 samples from 101 individuals showed evidence of a positive SARS-CoV-2 IgG test, with 33 samples available from 31 people living with HIV versus 70 samples from 70 people without HIV. 24 (77%) of 31 people with HIV were male sex at birth compared with 34 (49%) of 70 without HIV; median age was 50 years (IQR 40–56) and 51 years (43–58), respectively. 48 (48%) of 101 participants (18 with HIV and 30 without) with serology consistent with past SARS-CoV-2 infection had a previous positive PCR test documented within the health system (median 66 days [IQR 41–111] previously among people living with HIV vs 56 days [28–94] previously among people without HIV, $p=0.48$).

Among people living with HIV, the adjusted seroprevalence for SARS-CoV-2 IgG was 3.7% (95% CI 2.4–5.0) compared with 7.4% (5.7–9.2) in people without HIV (adjusted odds ratio [OR] 0.50, 95% CI 0.30–0.83). In the sensitivity analysis, if the test sensitivity were decreased to 70%, the seroprevalence would increase to 4.7% (95% CI 2.9–6.4) among people living with HIV and 9.4% (6.9–12.0) among those without HIV.

Adjusting for age, sex, race or ethnicity, and other chronic medical conditions, the odds of previous infection were 50% lower among people living with HIV (table 2). People of Latinx ethnicity had greater than six times higher odds of previous infection than non-Latinx White race, regardless of HIV status (table 2). Other chronic medical conditions were not associated with SARS-CoV-2 seropositivity (table 2). In the model exploring factors associated with SARS-CoV-2 IgG seropositivity among people living with HIV, a CD4 count of less than 200 cells per μL , unsuppressed viral load, and experiencing homelessness were not associated with SARS-CoV-2 seropositivity (table 2).

Although there were very few cases of severe COVID-19 overall (five [0.5%] among people living with HIV vs

two [0.2%] among those without HIV), among the 144 individuals with evidence of previous infection (IgG or PCR), the odds of severe COVID-19 were more than five times higher among people living with HIV adjusting for age and sex (adjusted OR 5.52, 95% CI 1.01–64.48).

	People with HIV (n=955)	People without HIV (n=1062)	p value for comparison
Sex at birth	<0.0001
Male	780 (81.7%)	517 (48.7%)	..
Female	175 (18.3%)	545 (51.3%)	..
Age, years	54 (46–63)	57 (50–66)	<0.0001
Race or ethnicity	<0.0001
White	345 (36.1%)	144 (13.6%)	..
Black	175 (18.3%)	94 (8.9%)	..
Latinx	253 (26.5%)	404 (38.0%)	..
Asian	138 (14.5%)	377 (35.5%)	..
Other	44 (4.6%)	43 (4.0%)	..
History of type 2 diabetes	210 (22.0%)	575 (54.1%)	<0.0001
History of cardiovascular disease	353 (37.0%)	595 (56.0%)	<0.0001
History of pulmonary disease	105 (11.0%)	96 (9.0%)	0.10
Median CD4 count, cells per μL	452 (249–656)
Unsuppressed HIV viral load >200 copies per mL	112 (11.7%)
Experiencing homelessness	155 (16.2%)

Data are n (%) or median (IQR) unless otherwise stated.

Table 1: Demographics of people living with HIV and the matched sample of people without HIV

	Adjusted odds ratio	95% CI	p value
Full cohort			
Male sex at birth	0.96	0.61–1.50	0.85
Age	0.97	0.95–0.98	<0.0001
Race or ethnicity vs White			
Black	1.82	0.62–5.29	0.27
Latinx	6.33	2.83–14.21	0.0001
Asian	0.92	0.32–2.62	0.88
Other	1.28	0.26–6.35	0.76
HIV	0.50	0.30–0.83	0.0080
History of type 2 diabetes	1.06	0.66–1.68	0.82
History of cardiovascular disease	0.83	0.57–1.45	0.69
History of pulmonary disease	0.50	0.18–1.42	0.20
People with HIV			
Male sex at birth	0.63	0.19–2.06	0.45
Age	0.99	0.95–1.03	0.54
Race or ethnicity vs White			
Black	0.43	0.05–3.95	0.46
Latinx	4.38	1.33–14.04	0.01
Asian	1.55	0.16–14.55	0.70
Other	1.57	0.16–15.31	0.58
Experiencing homelessness	0.87	0.17–4.44	0.87
CD4 count <200 cells per μL	0.45	0.08–2.46	0.42
Unsuppressed HIV viral load >200 copies per mL	1.87	0.42–8.37	0.42

Table 2: Factors associated with SARS-CoV-2 IgG seropositivity

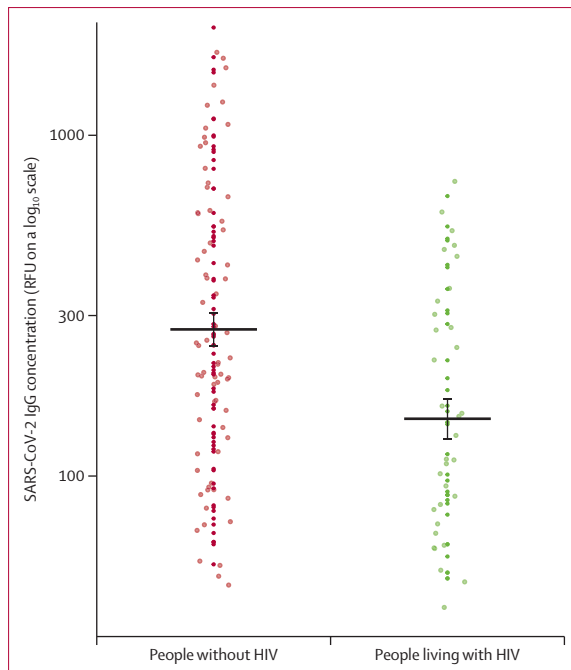


Figure 2: SARS-CoV-2 IgG concentrations compared between people living with HIV (n=31) and people without HIV (n=70)

The thick bars indicate the mean, and error bars indicate the SE. The relative mean was 42% (95% CI -16 to -59) lower in people with HIV than in those without HIV (adjusted for time since PCR-confirmed infection: -53%, 95% CI -4 to -76). Relative mean was calculated by log transforming IgG concentrations and then using mixed-effects linear regression adjusting for age, sex, and HIV status, with an indicator for the matched group included as a random effect. The same process was repeated with the inclusion of a variable for days since the date of PCR positivity for the 48 (48%) of 101 participants who had received a previous positive PCR test. RFU=relative fluorescent unit.

Among people living with HIV with severe COVID-19, three of five individuals had a CD4 cell count of less than 200 cells per μL , reflecting greater than 25 times odds of severe disease with low CD4 cell counts, although the CI was very wide given very few outcomes (OR 25.49, 95% CI 1.41–1805.02).

In people with evidence of SARS-CoV-2 seropositivity, adjusting for age and sex, SARS-CoV-2 IgG concentration was lower (percentage change -42%, 95% CI -16 to -59) among people with HIV than among those without HIV (figure 2). The following factors were not associated with a percentage change in IgG concentrations: age (7%, 95% CI -6 to 22, per 10 years); sex (-3%, -32 to 37); cardiovascular disease (-4%, -32 to 37); type 2 diabetes (29%, -10 to 83); and pulmonary disease (4%, -57 to 152). IgG concentrations were lower among people with CD4 counts of less than 200 cells per μL than among those with counts of 200 cells or more per μL , although the 95% CI was wide (percentage change -50%, 95% CI -81 to 29); unsuppressed viral load was not associated with IgG concentrations (10%, -56 to 280). For IgG pseudovirus neutralising antibodies, people living with HIV had lower titres than those without HIV (percentage change -53%, 95% CI -1 to -78; figure 3). Antibody avidity was similar between people living with

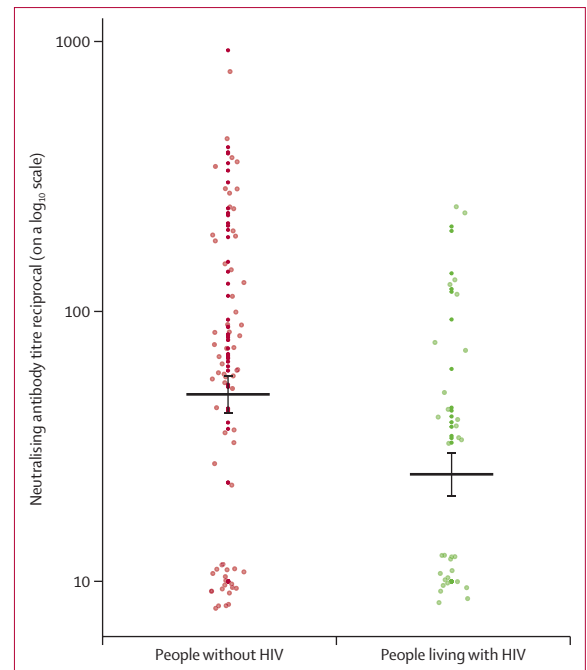


Figure 3: SARS-CoV-2 IgG pseudovirus neutralising antibody titres compared between people living with HIV (n=31) and people without HIV (n=70)

The thick bars indicate the mean, and error bars indicate the SE. The relative mean was 53% (95% CI -1 to -78) lower in people with HIV than in those without HIV (adjusted for time since PCR-confirmed infection: -67%, 95% CI -25 to -86). Relative mean was calculated by log transforming IgG concentrations and then using mixed-effects interval regression adjusting for age, sex, and HIV status, with an indicator for the matched group included as a random effect. The same process was repeated with the inclusion of a variable for days since infection based on the date of PCR positivity for the 48 (48%) of 101 participants who had received a previous positive PCR test.

HIV and those without HIV (percentage change 10%, 95% CI -28 to 48; figure 4).

In the individuals who had a previous PCR test confirming infection, analyses were additionally adjusted for time since the PCR test. Following this adjustment, IgG concentrations were lower among people living with HIV compared with those without HIV (percentage change -53%, 95% CI -4 to -76). For pseudovirus neutralising antibodies, titres were also lower among people with HIV than among those without HIV (percentage change -67%, 95% CI -25 to -86). Antibody avidity was similar among people with HIV compared with those without HIV (percentage change 7%, 95% CI -73 to 87). Natural log-transformed IgG concentrations and natural log-transformed pseudovirus neutralising antibody titres were correlated ($\rho=0.6$; $p<0.0001$); neutralising antibody titres and antibody avidity were negatively correlated ($\rho=-0.3$; $p=0.0060$); and IgG concentrations were not correlated with antibody avidity ($\rho=0.1$; $p=0.40$).

Discussion

In this study among outpatients in a municipal health-care system during the COVID-19 epidemic, seroprevalence of SARS-CoV-2 was about two times lower among people

living with HIV than among those without HIV. Overall, the seroprevalence for SARS-CoV-2 was less than 10% in both groups, reflecting the relatively controlled epidemic in San Francisco as compared with other sites in the USA. People living with HIV probably had fewer SARS-CoV-2 infections as a result of greater caution and sheltering in place, which in turn was probably attributable to higher perceived susceptibility, experience of the HIV epidemic, or both. Given that people with chronic medical conditions associated with severe COVID-19 other than HIV did not have reduced exposure to SARS-CoV-2, it is also possible that the additional services available to people living with HIV through the Ryan White Care Program (a US payor of last resort for those without insurance coverage) and other services (ie, food, housing, and psychosocial support) might have facilitated the ability of people living with HIV to shelter in place. Given the ongoing risk of COVID-19, these programmes should be continued or intensified. In addition, we observed a strong association between Latinx ethnicity and past SARS-CoV-2 infection, reflecting the known dynamics of the local (and national) epidemic.¹⁸ To avoid worsening disparities in the COVID-19 pandemic, SARS-CoV-2 vaccination should be targeted to the communities disproportionately affected.

Although there were only seven cases of severe COVID-19 in this cohort (hence this analysis should be considered exploratory), there were a greater number of severe cases of COVID-19 among people living with HIV despite fewer infections overall, compared with the sample of people without HIV. Three of the five cases of severe disease among people living with HIV occurred among individuals with low CD4 cell counts, similar to previous findings.^{10,11} The risk of severe disease among people living with HIV should be studied in larger population-based studies that account for possible differential testing and asymptomatic infection through systematic seroprevalence analysis.

The lower IgG concentrations and lower pseudovirus neutralising antibody titres among people living with HIV than among those without HIV in this study suggest a diminished response to natural SARS-CoV-2 infection, mirroring what is known about the serological response of people living with HIV to vaccines for other viral pathogens.^{19–23} Our findings contrast with Alrubayyi and colleagues' abstract, which did not find differences in IgG concentrations or pseudovirus neutralising titres by HIV status ($n=82$),²⁴ and Pallikkuth and colleagues' abstract, which did not find a difference in IgG concentrations by HIV status ($n=36$).²⁵ Differences in the source population (virally suppressed people living with HIV on antiretroviral therapy for at least 2 years in Alrubayyi and colleagues' abstract and all virally suppressed people living with HIV with a mean CD4 cell count of 859 cells per μL in Pallikkuth and colleagues' abstract) or our study design, which adjusted for potential confounders (age, sex, and time since infection), might explain the differences in our findings. People living with

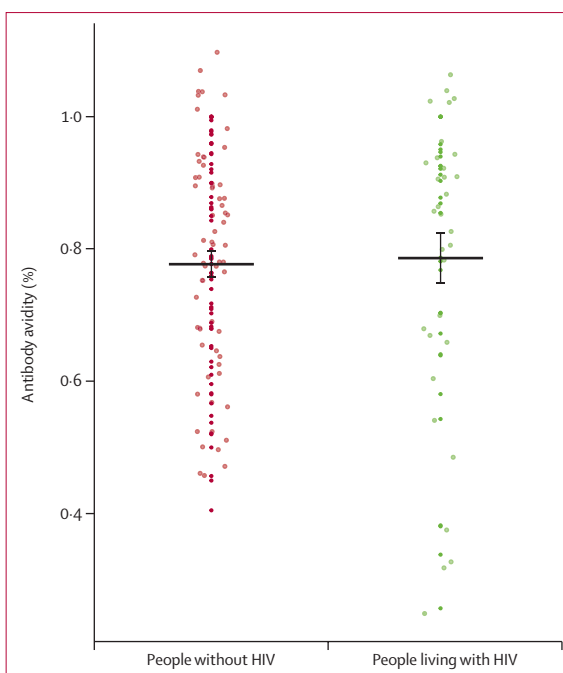


Figure 4: SARS-CoV-2 IgG percentage antibody avidity compared between people living with HIV ($n=31$) and people without HIV ($n=70$)

The thick bars indicate the mean, and error bars indicate the SE. The relative mean was 10% (95% CI –28 to 48) higher in people with HIV than in those without HIV (adjusted for time since PCR-confirmed infection: 7%, 95% CI –73 to 87). Relative mean was calculated using a mixed-effects generalised linear model from the binomial distribution adjusting for age, sex, and HIV status, with an indicator for the matched group included as a random effect. The same process was repeated with the inclusion of a variable for days since infection based on the date of PCR positivity for the 48 (48%) of 101 participants who had received a previous positive PCR test.

HIV show more rapidly waning neutralising antibody titres in response to yellow fever vaccination,²² respond less well to hepatitis B vaccination,^{19–21} and, depending on CD4 cells, do not mount equivalent immune responses to other vaccines.²³ This lack of durable neutralising antibody responses is thought to be mediated by lower CD4-to-CD8 cell ratios,²⁵ a chronic inflammatory state that can persist despite antiretroviral therapy, and altered germinal centre architecture.²⁶ The acute effects of SARS-CoV-2 infection include perturbations in immune function, most notably lymphopenia.^{27–29} People living with HIV might be particularly vulnerable to such effects, especially when total lymphocytes or CD4 lymphocytes are abnormal at baseline. Furthermore, lymphopenia can predict disease severity of COVID-19.³⁰ Finally, investigators from the Novavax COVID-19 vaccine South African sites reported that vaccine efficacy rose from 49% (95% CI 6–73) to 60% (20–80) when people living with HIV were excluded.³¹

The similar antibody avidity among people living with HIV compared with people without HIV could represent similar time from infection in this date of collection-matched outpatient cohort.¹⁵ Avidity responses might be less affected by disease severity in cohorts with a greater

proportion of asymptomatic infection.¹⁵ Future studies that seek to examine the immune response to infection should attempt to control for time since infection, as we did in this study.

This study has several limitations. The SARS-CoV-2 IgG used in this study showed excellent specificity with good durability, but lower sensitivity.¹³ Sensitivity might be lower in populations with greater numbers of asymptomatic infections than the population that provided samples for the validation study. Future studies should take into account test sensitivity and specificity. Moreover, a dual antibody approach, combining a higher sensitivity test as a screening test, could be considered. Given the relatively low seroprevalence in this study, test sensitivity probably played a smaller part than it would in higher prevalence settings, as shown by our sensitivity analysis. Systematic testing of remnant samples might not accurately represent the underlying population of people living with HIV or of people without HIV, and bias could result if subpopulations avoided presenting for outpatient laboratory testing differentially. Furthermore, participants who died as a result of COVID-19 would not be captured in our analysis, as they would not be able to present for follow-up testing. Our results should be considered reflective of the population engaged in outpatient care and using laboratory services in a municipal hospital. As the primary study goals were the comparison of people living with HIV versus those without HIV, rather than the absolute seroprevalence, potential bias is unlikely to have qualitatively affected our results. Overall, there were very few cases of severe disease and individuals with low CD4 counts with severe disease in this cohort, and these analyses should be considered exploratory. Last, we were unable to measure antibody temporal dynamics or anti-SARS-CoV-2 T-cell activity in our study, and had few individuals with previously PCR-confirmed infection. Future studies should characterise antibody temporal dynamics and the T-cell response among people living with HIV compared with people without HIV, including after vaccination.

In conclusion, people living with HIV had approximately two times lower seroprevalence of SARS-CoV-2 than people without HIV in an urban health-care system. Previous analyses might have inaccurately accounted for the ratio of infections to severe disease due to differential testing, although analyses should be repeated in larger population-based studies. Among people with confirmed infection, absolute IgG concentrations and pseudovirus neutralising antibody titres were lower among people living with HIV. People living with HIV should be followed up after vaccination, with antibody and T-cell activity measured when possible, to ensure they mount a sufficient immune response to prevent cases of severe COVID-19.

Contributors

MAS drafted the initial manuscript. MAS, MG, LBB, and MJP did the initial literature search. KLL and CY did the laboratory testing and method development. MAS and DVG analysed, had access to,

and verified all the data. MAS, KLL, CY, DVG, MJP, TJH, MG, and LBB reviewed and edited the manuscript, and provided substantial comments. MAS, MG, and LBB made the decision to submit for publication.

Declaration of interests

MAS, DVG, TJH, MG, and LBB report funding from the US National Institutes of Health during conduct of the study. DVG reports personal fees from Gilead Sciences outside the submitted work. All other authors declare no competing interests.

Data sharing

Data are not available for sharing.

Acknowledgments

This work was funded by the US National Institute of Allergy and Infectious Diseases, National Institutes of Health (R01AI158013).

References

- Brown LB, Spinelli MA, Gandhi M. The interplay between HIV and COVID-19: summary of the data and responses to date. *Curr Opin HIV AIDS* 2021; **16**: 63–73.
- Sachdev D, Mara E, Hsu L, et al. COVID-19 susceptibility and outcomes among people living with HIV in San Francisco. *J Acquir Immune Defic Syndr* 2021; **86**: 19–21.
- Chang JJ, Bruxvoort K, Chen LH, Rodriguez J, Akhavan B, Hechter RC. COVID-19 testing, characteristics, and outcomes among people living with HIV in an integrated health system. *Open Forum Infect Dis* 2020; **7** (suppl 1): S171–72.
- Huang J, Xie N, Hu X, et al. Epidemiological, virological and serological features of COVID-19 cases in people living with HIV in Wuhan City: a population-based cohort study. *Clin Infect Dis* 2020; published online Aug 17. <https://doi.org/10.1093/cid/ciaa1186>.
- Park LS, Rentsch CT, Sigel K, et al. COVID-19 in the largest US HIV cohort. *AIDS* 2020; 23rd International AIDS Conference Virtual; July 6–10, 2020 (abstr LBPEC23).
- Tesoriero JM, Swain CE, Pierce JL, et al. COVID-19 outcomes among persons living with or without diagnosed HIV infection in New York State. *JAMA Netw Open* 2021; **4**: e2037069.
- Inciarte A, Gonzalez-Cordon A, Rojas J, et al. Clinical characteristics, risk factors, and incidence of symptomatic COVID-19 in adults living with HIV: a single-center, prospective observational study. *AIDS* 2020; **34**: 1775–80.
- Del Amo J, Polo R, Moreno S, et al. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy: a cohort study. *Ann Intern Med* 2020; **173**: 536–41.
- Parmigiani A, Alcaide ML, Freguja R, et al. Impaired antibody response to influenza vaccine in HIV-infected and uninfected aging women is associated with immune activation and inflammation. *PLoS One* 2013; **8**: e79816.
- Dandachi D, Geiger G, Montgomery MW, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with HIV and coronavirus disease-19. *Clin Infect Dis* 2020; published online Sept 9. <https://doi.org/10.1093/cid/ciaa1339>.
- Boulle A, Davies MA, Hussey H, et al. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis* 2020; published online Aug 29. <https://doi.org/10.1093/cid/ciaa1198>.
- Papalini C, Paciosi F, Schiaroli E, et al. Seroprevalence of anti-SARS-CoV-2 antibodies in Umbrian persons living with HIV. *Mediter J Hematol Infect Dis* 2020; **12**: e2020080.
- Lynch KL, Whitman JD, Lacanienta NP, et al. Magnitude and kinetics of anti-SARS-CoV-2 antibody responses and their relationship to disease severity. *Clin Infect Dis* 2021; **72**: 301–08.
- Luo YR, Yun C, Chakraborty I, Wu AHB, Lynch KLA. SARS-CoV-2 label-free surrogate virus neutralization test and a longitudinal study of antibody characteristics in COVID-19 patients. *medRxiv* 2021; published online Jan 20. <https://doi.org/10.1101/2021.01.19.21250137> (preprint).
- Luo YR, Chakraborty I, Yun C, Wu AHB, Lynch KL. Kinetics of SARS-CoV-2 antibody avidity maturation and association with disease severity. *Clin Infect Dis* 2020; published Sept 14. <https://doi.org/10.1093/cid/ciaa1389>.

- 16 Lang Z, Reiczigel J. Confidence limits for prevalence of disease adjusted for estimated sensitivity and specificity. *Prev Vet Med* 2014; **113**: 13–22.
- 17 Grzelak L, Velay A, Madec Y, et al. Sex differences in the evolution of neutralizing antibodies to SARS-CoV-2. *J Infect Dis* 2021; published online March 7. <https://doi.org/10.1093/infdis/jiab127>.
- 18 Macias Gil R, Marcelin JR, Zuniga-Blanco B, Marquez C, Mathew T, Piggott DA. COVID-19 pandemic: disparate health impact on the Hispanic/Latinx population in the United States. *J Infect Dis* 2020; **222**: 1592–95.
- 19 van den Berg R, van Hoogstraten I, van Agtmael M. Non-responsiveness to hepatitis B vaccination in HIV seropositive patients; possible causes and solutions. *AIDS Rev* 2009; **11**: 157–64.
- 20 Collier AC, Corey L, Murphy VL, Handsfield HH. Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. *Ann Intern Med* 1988; **109**: 101–05.
- 21 Pasricha N, Datta U, Chawla Y, et al. Immune responses in patients with HIV infection after vaccination with recombinant hepatitis B virus vaccine. *BMC Infect Dis* 2006; **6**: 65.
- 22 Avelino-Silva VI, Miyaji KT, Hunt PW, et al. CD4/CD8 ratio and KT ratio predict yellow fever vaccine immunogenicity in HIV-infected patients. *PLoS Negl Trop Dis* 2016; **10**: e0005219.
- 23 Kroon FP, van Dissel JT, Labadie J, van Loon AM, van Furth R. Antibody response to diphtheria, tetanus, and poliomyelitis vaccines in relation to the number of CD4+ T lymphocytes in adults infected with human immunodeficiency virus. *Clin Infect Dis* 1995; **21**: 1197–203.
- 24 Alrubayyi AS, Gea-Mallorqui E, Touizer E, HameiriBowen D, Kopycinski D, Charlton B. Characterization of SARS-CoV-2 specific responses in people living with HIV. Conference on Retroviruses and Opportunistic Infections; virtual; June 3–Nov 3, 2021 (abstr 252).
- 25 Pallikkuth S, Sharkey M, Beauchamps L, Raccamarich P, Uribe C, Salazar A. Persistence of SARS-CoV-2-specific Ab response in HIV+ individuals on ART. Conference on Retroviruses and Opportunistic Infections; virtual; June 3–Nov 3, 2021 (abstr 260).
- 26 Moysi E, Pallikkuth S, De Armas LR, et al. Altered immune cell follicular dynamics in HIV infection following influenza vaccination. *J Clin Invest* 2018; **128**: 3171–85.
- 27 Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; **395**: 514–23.
- 28 Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. *AJR Am J Roentgenol* 2020; **215**: 87–93.
- 29 Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934–43.
- 30 Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020; **5**: 33.
- 31 Callaway E, Mallapaty S. Novavax offers first evidence that COVID vaccines protect people against variants. *Nature* 2021; **590**: 17.